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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,499	05/04/2001	Herman Waldmann	1324.028	8699

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EXAMINER	
TON, THAIAN N	
ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 08/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/849,499	Applicant(s) WALDMANN ET AL.	
	Examin r Thaian N. Ton	Art Unit 1632	

-- Th MAILING DATE of this communication appears on th cov r she t with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64-109* is/are pending in the application.

4a) Of the above claim(s) *96-104 and 109* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64-95 and 105-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Preliminary Amendment, filed 10/09/01, Paper No. 5, has been entered. Claims 81, 86 and 104 have been amended. Claims 105-109 have been added.

Claims 64-109 are pending. Claims 64-95 and 105-108 are under current examination.

Election/Restrictions

Applicant's election without traverse of Group I, claims 64-95 and 105-108, in Paper No. 8 is acknowledged.

Claims 96-104 and 109 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8, filed 5/8/02.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.

(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)

(e) BACKGROUND OF THE INVENTION.

(1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) BRIEF SUMMARY OF THE INVENTION.

(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).

(h) DETAILED DESCRIPTION OF THE INVENTION.

(i) CLAIM OR CLAIMS (commencing on a separate sheet).

(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).

(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claim Objections

Claim 69 is objected to because of the following informalities: The claim recite "he" in the first word of the claim. It appears that the word should read "The". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64-95 and 105-108 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention consists of methods for producing long-term culture of immature dendritic cells which comprises providing a population of embryonic stem cells [specifically the ESF116 mouse embryonic stem cell line], culturing the embryonic stem cells in the presence of a cytokine or combination of cytokines which bring about differentiation of the embryonic stem cells into immature dendritic cells to produce a long-term culture of immature dendritic cells and recovering immature dendritic cells from the culture, which immature dendritic cells are capable of maturation to an immunostimulatory phenotype. Since the ESF116 mouse embryonic stem cell line is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. It is noted that Applicant has deposited the cell line under the terms of the Budapest Treat [see p. 11, lines 25-30 of the specification]. As the deposit is made under the terms of the Budapest Treaty, an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific cell line have been deposited under the Budapest Treaty and that the cell line will be irrevocably and without

restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

Claims 65-95 and 105-108 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a long-term culture of immature dendritic cells wherein the method comprises culturing ES cells from the mouse embryonic stem cell line ESF116 in the presence of murine IL-3 [and optionally, murine GM-CSF] to bring about differentiation of the ES cells into immature dendritic cells and stimulating the maturation of the immature dendritic cells with LPS, does not reasonably provide enablement for methods for producing long-term cultures of immature dendritic cells utilizing any population of ES cells, for the breadth claimed, culturing the ES cells in the presence of any cytokine or combination of cytokines to bring about the differentiation of the ES cells into immature dendritic cells to produce a long-term culture of immature dendritic cells, and stimulating the mature of the immature dendritic cells with any inflammatory mediator. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is broadly directed to methods for producing long-term cultures of immature dendritic cells comprising culturing a population of ES cells in the presence of a cytokine or combination of cytokines, which brings about the

differentiation of the ES cells into immature dendritic cells to produce a long-term culture of immature dendritic cells. In further embodiments, the claimed invention is directed to the maturation of the immature dendritic cells utilizing an inflammatory mediator, such as LPS. The claimed invention is further directed to the production of immature dendritic cells by the above-described method, wherein the ES cells are genetically modified with heterologous genes, which encode, for example, the Fas-ligand, antigen targets for the immune system, such as an autoantigen, a tumour antigen, or a foreign antigen, anti-apoptotic genes, FLIP or bcl-2 or reporter genes, such as GFP.

The specification teaches that the mouse embryonic stem cell line, ESF116 was cultured in the absence of exogenous LIF to produce embryoid bodies. These embryoid bodies were then cultured in an ES medium supplemented with recombinant murine IL-3 and tissue culture supernatant containing murine GM-CSF. After 4 days of culture, cells with dendritic cell [DC] morphology appeared [see Figure 1b-c]. These ES cell-derived DCs [esDC] were then harvested and maintained in culture for at least 5 weeks [see Examples 1-2]. The specification further teaches that IL-3 is indispensable for the generation of the esDCs, however, the presence of GM-CSF is not required for the generation of esDCs. Cells which were cultured in only IL-3 produced esDCs which represented lymphoid DC [see Example 3]. The esDCs were characterized and found to be immature dendritic cells. These esDCs were then matured utilizing the inflammatory mediator, LPS

and it was found that the resulting cells showed the morphology characteristic of mature DC [see Example 4]. The specification further teaches that the ESF116 cell line was transfected with an expression vector containing GFP and stable clones selected for the generation of esDC [Example 5]. The specification further teaches that the ESF116 cell line was transfected with a vector consisting of the murine CD11c promoter operably linked to a rabbit beta-globin fragment [Example 6]. The specification teaches that the ESF116 cell line was transfected with a construct encoding the Fas-ligand gene to generate DCs constitutively expressing the protein [Example 7].

The specification fails to give an enabling disclosure for methods for producing a long-term culture of immature dendritic cells by culturing any ES cells, for the breadth claimed, with any cytokine or combination thereof for the breadth claimed. In particular, the specification does not provide guidance or teachings to show that any other ES cell line with any particular cytokine would be capable of differentiating into immature dendritic cells. In fact, the specification teaches that until the time the claimed invention was made, although hematopoiesis was observed following ES cell differentiation, primary dendritic cells have not been observed. The specification teaches that even in cases wherein IL-3, with or without the addition of GM-CSF, was used to induce hematopoiesis in ES cells, no DC development was reported [see p. 5, lines 5-12]. Furthermore, the specification teaches that the apparent inconsistency in the previous results and the results

presented by the specification is dues to differences in protocols, as well as strain differences between the propensity of ES cells to support development of DC cells [see p. 8, lines 19-30]. Furthermore, with regard to particular cytokines used in the process to differentiate the ES cells, the specification teaches that, "Significantly, of all the combinations of cytokines tested, only GM-CSF and IL-3 have been found to have the capacity to support DC development." [See p. 5, lines 10-11].

Accordingly, in view of the quantity of experimentation necessary for the production of long-term cultures of immature dendritic cells by culturing any ES cells with any cytokine [or combination thereof], the lack of guidance, teachings and examples provided by the specification for the production of long-term cultures of immature dendritic cells from any ES cells with any cytokine, other than the exemplified ESF116 murine ES cell line with IL-3 [and optionally murine GM-CSF], as well as the unpredictable state of the art with regard to the availability of ES cells lines capable of supporting DC development, and the requirement for IL-3 for differentiation, it would have required undue experimentation for one skilled in the art to make and/or use the claimed long-term cultures of dendritic cells and methods of making the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 65-95 and 105-108 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 64, as written, is incomplete. It is unclear how differentiation of the ES into immature dendritic cells in part (ii) of the claim results in a long-term culture of immature dendritic cells. The claim is further vague because recites that the immature dendritic cells are capable of maturation to an "immunostimulatory phenotype." It is unclear what this term encompasses. Claims 65-95 and 105-108 depend from claim 64.

Claim 65, as written, is unclear. The claim recites "stimulating" the immature dendritic cells to mature, however, it is unclear what the term "stimulating" encompasses. Claims 66-67 depend from claim 65.

Claim 70, as written, is incomplete. The claim recites that the ES cells in (i) of claim 64 are in the form of embryoid bodies. However, the claim does not provide steps to show the formation of embryoid bodies from the population of embryonic stem cells, for example, culturing steps would be required for a population of ES cells to produce an embryoid body.

Claim 73, as written, is vague. The claim recites the term, "immunomodulatory effect" in line 2 of the claim. However, it is unclear what this term encompasses, or what sorts of immunomodulatory effects. Claims 74, 75, 77 depend from claim 73.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

TNT

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